UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,988	10/07/2003	Andrew Robert Marks	19240-593-US1	6477

56949 7590 02/27/2007
WilmerHale/Columbia University
399 PARK AVENUE
NEW YORK, NY 10022

EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	**Application No.** 10/680,988	**Applicant(s)** MARKS ET AL.
	Examiner Ruixiang Li	**Art Unit** 1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-14 and 16-42* is/are pending in the application.

4a) Of the above claim(s) *19-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 11-14, 16-18, 41, and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date *See Continuation Sheet*.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :07/12/2004; 08/08/2006; 10/20/2006.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-18, in the reply filed on 11/20/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
2. Applicants' preliminary amendment filed on 11/20/2006 has been entered in full. Claims 10 and 15 have been canceled. Claims 41 and 42 have been added. Claims 1-9, 11-14, and 16-42 are pending. Claims 1-9, 11-14, 16-18, 41, and 42 are under consideration. All other claims are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Information Disclosure Statement

3. The information disclosure statements filed on 07/12/2004, 08/08/2006, and 0/20/2006 have been considered by the examiner and a signed copy has been attached to this office action

Drawings

4. The drawings filed on 11/07/2003 are accepted.

Priority

5. The subject matter defined in claims 1-9, 11-14, 16-18, 41, and 42 has been determined to have an effective filing date of October 7, 2003, which is the filing date of the instant application. All parent applications fail to provide adequate support under 35 USC *112* for the instantly claimed invention.

Claim Rejections—35 USC § 112, 1st paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-9, 11-14, 16-18, 41, and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for preventing arrhythmias and sudden cardiac death in FKBP12.6+/- mice or limiting a decrease in the level of RyR2-bound FKBP12.6 in a subject, does not reasonably provide enablement for a method for preventing arrhythmias and sudden cardiac death in any other subjects or prevent a decrease in the level of RyR2-bound FKBP12.6 in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 1-9 and 18 are drawn to a method for limiting or preventing a decrease in the level of RyR2-bound FKBP12.6 in a subject who is a candidate for exercise-induced cardiac arrhythmia, claims 11-14 and 41 are drawn to a method for treating or preventing exercise-induced cardiac arrhythmia in a subject, whereas claims 16, 17, and 42 are drawn to a method for preventing exercise-induced sudden cardiac death in a subject. Thus, the claimed invention encompasses a method of preventing exercise-induced cardiac arrhythmia or sudden cardiac death in a subject.

However, the specification merely discloses that JTV-519 prevents arrhythmias and sudden cardiac death in FBBP12.6+/- mice by rebinding FKBP12.6 to RyR2 (see, e.g. Fig. 1; page 10, lines 14-16 of the specification). There is no evidence showing that JTV-519 prevents arrhythmias and sudden cardiac death in any other subjects. There are no sufficient guidance and/or working examples regarding preventing arrhythmias and sudden cardiac death in subjects other than FBBP12.6+/- mice. It is unpredictable whether JTV-519 would completely prevent arrhythmias and sudden cardiac death in a subject other than FBBP12.6+/- mice. In fact, the art teaches that JTV-519 improved left ventricular systolic and relaxation functions and led to less severe heart failure in a canine model (Yano et al. (*Circulation* 107:477-484, 2003). Yano et al. also teach that in JTV-519-treated hearts, both the stoichiometry of FKBP12.6 binding to RyR and the amount of RyR-bound FKBP12.6 were restored toward the values seen in normal sarcoplasmic reticulum (see, Abstract and Table 2). Moreover, the level of phosphorylated RyR in JTV-519 treated hearts was returning toward the levels seen in normal hearts (see, e.g., Abstract).

Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

It is suggested that the word "preventing" be deleted from the claims to overcome the rejections. Alternatively, the subject recited in the claims is limited to FBBP12.6+/- mice.

8. Claims 1-9, 18, 41, and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 1-9 and 18 are drawn to a method for limiting or preventing a decrease in the level of RyR2-bound FKBP12.6 in a subject, whereas claims 41 and 42 are drawn to a method for treating or preventing exercise-induced cardiac arrhythmia or sudden cardiac death in a subject comprising administering JTV-519 to the subject an amount of JTV-519 effective to limit or prevent a decrease in the level of RyR2 bound FKBP12.6 in the subject. Thus, the claims encompass not only FKBP12.6 protein but also its analogues (see [0031] of specification). However, the instant disclosure fails to disclose any FKBP12.6 analogues that are functional variants of the FKBP12.6 protein. The prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed FKBP12.6 analogues. Therefore, only the method that encompasses FKBP12.6 protein, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections Under 35 U. S. C. § 103 (a)

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-9, 11-14, 16-18, 41, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yano et al. (*Circulation* 107:477-484, January 28, 2003), in view of Wehrens et al., Cell 113:829-840, June 27, 2003)

Yano et al. teach the development of heart failure is tightly correlated with a decrease in the stoichiometric ratio for FKBP12.6 binding to the ryanodine receptor (RyR) in the sarcoplasmic reticulum (SR). JTV-519 reverses this pathogenic process and has a protective effect against Ca2+ overload-induced myocardial injury (see beginning of the Abstract).

Yano et al. teach that in a canine model of heart failure that was produced by 4 weeks of rapid right ventricular pacing with or without JTV519, no signs of heart failure in JTV-519-treated dogs (12 mg/kg per day; see left column of page 478) were observed after 4 weeks of chronic right ventricular pacing, and left ventricular remodelling was prevented (see, e.g., Abstract). Moreover, JTV-519 acutely inhibited both the FK506-induced Ca2+ leak from RyR in normal SR and the spontaneous Ca2+ leak in failing SR. There was no abnormal Ca2+ leak in SR vesicles isolated from JTV-519-treated hearts. Furthermore, both the stoichiometry of FKBP12.6 binding to RyR and the amount of RyR-bound FKBP12.6 in JTV-519-treated hearts were restored toward the values seen in normal SR. Additionally, RyR was PKA-hyperphosphorylated in JTV-519-untreated hearts, whereas it was reversed in JTV-519-treated hearts, returning the channel phosphorylation toward the levels seen in normal hearts.

Yano et al. do not explicitly teach (i) treating exercise-induced cardiac arrhythmia or sudden cardiac death and (ii). a human subject.

Wehrens et al. teach FKBP12.6 deficiency and defective calcium release channel (ryanodine receptor) function linked to exercise-induced sudden cardiac death. Wehrens et al. also teach that during exercise, RyR2 phosphorylation by cAMP-dependent protein kinase A (PKA) partially dissociates FKBP12.6 from the channel, increasing intracellular Ca2+ release and cardiac contractility. Wehrens et al. further teach mutations in RyR2 linked to exercise-induced arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) reduced the affinity of FKBP12.6 for RyR2 and increased single-channel activity under conditions that simulate exercise (see, e.g., Abstract).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to treat exercise-induced cardiac arrhythmia or sudden cardiac death in a subject, including a subject with CPVT, by administering to the subject a therapeutically effective amount of JTV-519 with a reasonable expectation of success. One would be motivated to do so because JTV-519 has the capability of reversing the process of dissociation of FKBP12.6 from RyR2 receptor and reducing the abnormal Ca2+ leak through RyR2, as shown by Yano et al. (see, e.g., Abstract).

It would also have been obvious to one having ordinary skill in the art at the time the invention was made to treat a human subject by administering to the human subject a therapeutically effective amount of JTV-519 with a reasonable expectation of success. It is a logical and obvious step for one of skill in the art to treat a human subject after a drug is tested successfully in an animal model.

11. Claims 1-3, 5-9, 11, 13, 14, 16, 18, 41, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yano et al. (*Circulation* 107:477-484, January 28, 2003).

Yano et al. teach the development of heart failure is tightly correlated with a decrease in the stoichiometric ratio for FKBP12.6 binding to the ryanodine receptor (RyR) in the sarcoplasmic reticulum (SR). JTV-519 reverses this pathogenic process and has a protective effect against Ca2+ overload-induced myocardial injury (beginning the Abstract).

Yano et al. teach that in a canine model of heart failure that was produced by 4 weeks of rapid right ventricular pacing with or without JTV519, no signs of heart failure in JTV-519-treated dogs (12 mg/kg per day; see left column of page 478) were observed after 4 weeks of chronic right ventricular pacing, and left ventricular remodelling was prevented (see, e.g., Abstract). Moreover, JTV-519 acutely inhibited both the FK506-induced Ca2+ leak from RyR in normal SR and the spontaneous Ca2+ leak in failing SR. There was no abnormal Ca2+ leak in SR vesicles isolated from JTV-519-treated hearts. Furthermore, both the stoichiometry of FKBP12.6 binding to RyR and the amount of RyR-bound FKBP12.6 in JTV-519-treated hearts were restored toward the values seen in normal SR. Additionally, RyR was PKA-hyperphosphorylated in JTV-519-untreated hearts, whereas it was reversed in JTV-519-treated hearts, returning the channel phosphorylation toward the levels seen in normal hearts.

Yano et al. do not explicitly teach (i) treating exercise-induced cardiac arrhythmia or sudden cardiac death and (ii). a human subject.

However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to treat exercise-induced cardiac arrhythmia or sudden cardiac death in a subject by administering to the subject a therapeutically effective amount of JTV-519 with a reasonable expectation of success. One would be motivated to do so because both exercising and pacing that simulates exercise produce stress that induces heart failure.

It would also have been obvious to one having ordinary skill in the art at the time the invention was made to treat a human subject by administering to the human subject a therapeutically effective amount of JTV-519 with a reasonable expectation of success. It is a logical and obvious step for one of skill in the art to treat a human subject after a drug is tested successfully in an animal model.

Conclusion

12. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

Ruixiang Li

Ruixiang Li, Ph.D.
Primary Examiner
February 19, 2007

RUIXIANG LI, PH.D.
PRIMARY EXAMINER